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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/125,122	01/04/1999	GIULIO TARRO	A31920-PCT-U	7447

21003 7590 02/27/2003

BAKER & BOTTS
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	27

DATE MAILED: 02/27/2003

Remail

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No. 09/125,122	Applicant(s) TARRO ET AL.	
	Examiner Bridget E. Bunner	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,9,11,13,15 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9,11,13,15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 24 June 2002 (Paper No. 23) has been entered in full. Claim 7 is amended and claim 20 is cancelled

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 7, 9, 11, 13, 15,and 17 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 2 of the previous Office Action (Paper No. 21, 20 December 2001) are *withdrawn* in view of the amended title (Paper No. 23, 24 June 2002).

2. The rejections to claims 7, 9, 11, 13, 15, 17, and 20 under 35 U.S.C. 112, second paragraph, as set forth at pg 3 of the previous Office Action (Paper No. 21, 20 December 2001) are *withdrawn* in view of the amended claims (Paper No. 23, 24 June 2002).

3. The rejection of claim 20 under 35 U.S.C. § 102(b) as set forth at pg 3-4 of the previous Office Action (Paper No. 21, 20 December 2001) are *withdrawn* in view of the cancelled claim (Paper No. 23, 24 June 2002).

Claim Rejections - 35 USC § 103

4. Claims 7, 11, 13, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Di Bisceglie et al. (New England J Med 321: 1506-1510, 1989) in view of either one of Cummins (U.S. Patent No. 5,824,300) or Cummins et al. (WO 88/03411).

Applicant's arguments (Paper No. 23, 24 June 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the claims of the instant application are not obvious. Applicant argues that there is no motivation to combine the references relating to interferon use for the treatment of a wide variety of diseases which do not specifically include hepatitis C infection. Applicant contends that the Cummins references focus on disorders primarily affecting the immune system. Applicant also argues that Cummins '300 and '411 state that the disclosed methods may be used to treat human and animal infections, and provide examples of viruses which could be treated. Applicant asserts that the Cummins references do no mention hepatitis C. Applicant continues to add that Di Bisceglie et al. relates specifically to hepatitis C. However, Applicant submits that Di Bisceglie et al. is a later reference than the Cummins references and teaches not to use lower doses as taught by the Cummins references. Applicant asserts that there is no suggestion to combine the references and the rejection should be removed.

Applicant's arguments have been fully considered but are not found to be persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Cummins references are not required to mention hepatitis C since Di Bisceglie et al. discloses treatment of hepatitis C by α-interferon. Furthermore, Di Bisceglie et al. is a later reference than the Cummins '300 and '411 patents, but these references are earlier than the priority date of the instant application and teach all of the claim limitations. Additionally, although Di Bisceglie treats patients with higher doses of α-interferon than the dosage range recited in the claims and recommends increasing the dosage in future studies (see pg 1510), Di Bisceglie et al. does not specifically disclose that

lower doses of α-interferon would not treat subjects with hepatitis C. In other words, Di Bisceglie et al. does not teach that administration of α-interferon to subjects with hepatitis C at a low dose is ineffective.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to prepare a liquid formulation containing human leukocyte α-interferon for oral administration to treat a subject having hepatitis C is disclosed in Cummins '300 (col 4, lines 8-53) and Cummins '411 (pg 8-9). The Cummins references teach that interferon contacting the oral and pharyngeal mucosa is consistently efficacious for the treatment of diseases to which the immune system of many warm-blooded vertebrates does not effectively respond (Cummins '300, col 4, lines 15-19; Cummins '411, pg 8, lines 6-12). The Cummins references also disclose that "contact of interferon with the oral and pharyngeal mucosa and thereafter with the lymphatic system of the treated human or animal is unquestionably the most efficient method administering immunotherapeutic amounts of interferon" (Cummins '300, lines 49-53; Cummins '411, pg 9, lines 11-15).

(ii) Applicant asserts that even the references were combined, they convey no expectation of success. Applicant states that the Cummins references are broad and general disclosures and do

not mention treatment of hepatitis C. Applicant indicates that Di Bisceglie et al. is directed toward hepatitis C, is published approximately 1.5 years after Cummins '300, and is recommending that a weekly dosage of greater than 6 million units of interferon be used in clinical trials. Applicant contends that the highest weekly dose of α-interferon covered by the claims is 3500 units and that Di Bisceglie et al. administer α-interferon subcutaneously. Applicant questions why the skilled artisan would reasonably expect the low oral dose claimed to be successful. Applicant argues that since Cummins '300 was in the public domain 1.5 years before Di Bisceglie et al. was published, the scientists involved in the NIH clinical trial should have been aware of Cummins '300 and yet, did not recommend a lower dose. Applicant cites the NIH Consensus Statement 15(3):1-41, 1997 to emphasize that a formal review of the art by clinical authorities performed at the approximately the same time the invention was made did not find it obvious to administer low-dose oral α-interferon for the treatment of hepatitis C, but rather recommended a higher subcutaneous dose be used.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, as discussed above, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. Di Bisceglie et al. teaches daily subcutaneous administration of human α-interferon to subjects having type C viral hepatitis. Each of the Cummins references disclose aqueous formulations of human α-interferon for oral delivery. The Cummins references also teach that for typical patients weighing from about 100 to 225 pounds (*ca.* 45-100 kg), the preferred dosages are thus on the order of 50 to 340 IU α-interferon per day. Among the preferred sources of α-interferon are buffy coat leukocytes ('300, col. 3, lines 25-35; '411, page 4, lines 2-6). Other exemplary formulations described by

Cummins contain 1-1500 IU of α-interferon in a dosage volume of one tablespoon (15 ml), or 0.07-100 IU ml^{-1} of cough syrup ('300 at col. 14, lines 1-5; '411 at page 31, first full paragraph). In combination, Di Bisceglie et al. and the Cummins references teach the limitations recited in the claims of the instant application. Although scientists involved in the NIH clinical trial recommended a higher dose of α-interferon be administered to hepatitis C patients, the NIH Consensus Statement does not teach that administration of α-interferon to subjects with hepatitis C at a low dose is totally ineffective.

5. Claims 9 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Di Bisceglie et al. and either one of Cummins '300 or '411 as applied to claims 7, 11, 13, and 17 above, further in view of Ratajczak et al. (Arch. Immunol. Ther. Exp. 41: 237-40, 1993).

Applicant's arguments (Paper No. 23, 24 June 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that for the same reasons set forth regarding the rejection of claims 7, 11, 13, and 17, Applicant concludes that claims 9 and 15 are not obvious. Applicant contends that the mere disclosure that α-interferon could be incorporated in a lozenge for treating a disease caused by a distinct viral agent (hepatitis B) rather than hepatitis C does not render obvious the combination of the Cummins references and Di Bisceglie et al.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed above, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In*

re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Ratajczak et al. is not required to teach all of the limitations of the claims. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare an aqueous formulation of human α-interferon according to Cummins '300 or '411, employing lymphoblastoid α-interferon as described by Ratajczak in place of the buffy coat leukocyte α-interferon noted particularly by Cummins, because Ratajczak evidences that lymphoblastoid interferon was readily available at the time of the invention and teaches that it is suitable for the treatment of an exemplary viral disease *via* delivery to the oropharyngeal mucosae. It consequently would have been obvious to the artisan that lymphoblastoid interferon would be the functional equivalent of the human α-interferon liquid preparations expressly described by Cummins in the '300 and '411 references for use in the treatment of subjects having type C viral hepatitis as described in Di Bisceglie et al.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
September 10, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER